Molecular Cancer

REVIEW

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Caveolin-1: an ambiguous entity in breast cancer

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Abstract

Breast cancer (BC) is the most frequently diagnosed cancer in women and the second leading cause of death from cancer among women. Metastasis is the major cause of BC-associated mortality. Accumulating evidence implicates Caveolin-1 (Cav-1), a structural protein of plasma membrane caveolae, in BC metastasis. Cav-1 exhibits a dual role, as both a tumor suppressor and promoter depending on the cellular context and BC subtype. This review highlights the role of Cav-1 in modulating glycolytic metabolism, tumor-stromal interactions, apoptosis, and senescence. Additionally, stromal Cav-1's expression is identified as a potential prognostic marker, offering insights into its contrasting roles in tumor suppression and progression. Furthermore, Cav-1's context-dependent effects are explored in BC subtypes including hormone receptor-positive, HER2-positive, and triple-negative BC (TNBC). The review further delves into the role of Cav-1 in regulating the metastatic cascade including extracellular matrix interactions, cell migration and invasion, and premetastatic niche formation. The later sections discuss the therapeutic targeting of Cav-1 by metabolic inhibitors such as betulinic acid and Cav-1 modulating compounds. While Cav-1 may be a potential biomarker and therapeutic target, its heterogeneous expression and context-specific activity necessitates further research to develop precise interventions. Future studies investigating the mechanistic role of Cav-1 in metastasis may pave the way for effective treatment of metastatic BC.

Keywords Breast Cancer, Metastasis, Caveolin-1, Prognosis, Anti-Cav-1 therapy

Introduction

Breast cancer (BC) is a significant health challenge on a global scale accounting for approximately 11.7% of the total cancer cases and 6.9% of cancer-related deaths worldwide [1]. In the United States alone, nearly 3.8 million women were diagnosed with BC at the beginning of 2019 [2]. Despite the recent decline in BC mortality especially in the hormone and human epidermal growth factor receptor 2 ($HER2^+$) BC cases, it remains the most diagnosed cancer in women and the second leading cause of cancer-associated deaths in women. Unfortunately, the persistent mortality rate is often associated with metastasis which is reported in nearly 20–30% of patients with BC [3].

Metastasis, one of the hallmarks of cancer, is the cause of approximately 90% of cancer-related deaths [4–7]. Metastasis is a multifaceted process that enables the growth of cancer cells at distant organ sites away from the primary site where the tumor originated [8–10]. Accumulating evidence has shown that BC metastasis is associated with compromised membrane integrity [8, 11–13].

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Caveolae are specialized hydrophobic microdomains of the plasma membrane that are generated by a protein called caveolin (Cav). Besides its role in many cellular functions [14–20], caveolin is also linked to BC metastasis [8, 21–23]. Recently, our studies have shown that caveolin-1 (Cav-1) knockout (KO) mitigated BC metastasis to lungs via integrin (ITG)-α3 dysregulation in the 4T1-induced syngeneic BC model [8].

Although role of Cav-1 in regulating a variety of cellular functions, and BC progression is widely reported (Table 1), there is a gap in the existing knowledge regarding the mechanistic role of Cav-1 in metastasis. This review aims to provide a comprehensive understanding of the aberrant regulation of Cav-1 in BC metastasis. Herein, the role of Cav-1 in a wide array of cellular functions including metabolism, autophagy, apoptosis and senescence, cell cycle progression, and immune regulation are discussed. Next, the review delves into the complex role of Cav-1 in molecular subtypes of BC-estrogen receptor $(ER)^+$ signaling, $HER2^+$, and triple-negative breast cancer (TNBC). In addition, the review summarized previous reports by critical evaluation of prior research to understand the intricate association between Cav-1 and the metastatic cascade signaling. Furthermore, Cav-1 is clinically relevant as we reviewed numerous studies that linked Cav-1 expression in BC patients suggesting that targeting Cav-1 may be a novel approach in the treatment of BC.

BC is a complex heterogeneous disease with distinct metastatic patterns depending on molecular subtypes [24, 25]. According to the 2013 St. Gallen consensus criteria which took into account the status of estrogen receptor (ER), progesterone receptor (PR), (HER2); and Ki67 index, BC subtypes included luminal A (ER/PR^+, $HER2^-$, $Ki67^+ < 20\%$); luminal B (ER/PR^+, $HER2^-$, $Ki67^+ \geq 20\%$; ER/PR^+, HER2-enriched); HER2-enriched (ER^-, PR^-, HER2-enriched); and basal-like triple-negative breast cancer (TNBC) [26].

In addition, Lehmann et al. [27] subcategorized TNBC into basal-like (BL1 and BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR) types. Based on the Ki67 index, luminal B cancers are more aggressive with less favorable clinical outcomes as compared to luminal A. On the other hand, HER2-enriched and TNBC are more aggressive with poorer prognosis than luminal cancers [25]. Due to its unique molecular phenotype, TNBC is highly invasive compared to other subtypes with distant metastasis as reported in ~ 46% of the patients [28].

Despite significant advances such as endocrine therapy for ER/PR^+ [29, 30], targeted therapies for $HER2^+$ [31, 32], and systemic chemotherapy for TNBC [27,

Table 1 Summary of the biology associated with Cav-1. [8, 68, 70, 73, 83, 87, 89, 93, 93, 95, 107, 110, 113, 128–130, 132, 135, 140, 144, 160, 162, 178, 204, 212, 213]

Biology	Comments	Organisms/cell lines	References
Cellular metabolism	Interaction of Cav-1 with IGF-1R/IR and LRP6 induced aerobic glycolysis	LNCaP prostate cancer cells	[68]
	Cav-1 silencing decreased the levels of 3-phosphoglycerate, fructose-6-phosphate, and glucose-6-phospate	BAEC bovine aortic endothelial cells	[70]
	Ectopic expression of Cav-1 downregulated NRF2 and MnSOD	MCF-7 BC cells	[73]
Autophagic tumor stroma	Proteomic analysis of Cav-1 depleted fibroblast resulted in upregulation of collagen VI (COL6A1, COL6A2)	human	[83]
	Interaction of Cav-1 with LC3 and ATG12/5 prevents autophagasome formation	mice, lung epithelial Beas-2B cells	[93], [89]
	Cav-1 silencing downregulated HMGB1, LC3-II, ATG12/5	BT-474 BC cells	[93]
Apoptosis and cell sensescence	pY14Cav-1 induced sensitivity to paclitaxel	MCF-7 BC cells	[95]
	Cav-1 sequesters Mdm2 to upregulate p21 via stabilization of p53	human fibroblasts, MEFs	[107]
Cell cycle progression	Transfection of Cav-1 resulted in Go/G1 phase arrest	murine fibroblast NIH 3T3 cells	[110]
	Cav-1 depletion hyperactivated p42/44 MAP kinase signaling	murine fibroblast NIH 3T3 cells	[113]
Immune regulation	CSD of Cav-1 binds to CD26/DPPIV to induce TT-specific T cell activation	human monocytes	[128]
	Cav-1(-/-) resulted in eNOS activity and reduced NF-kB activation	mice	[130]
	Cav-1 colocalized with TLR4 to induce inflammatory response during gram-negative bacterial infection	mice	[129]
Extracellular vesicles	Presence of Cav-1 in EV determined the presence of tenascin and Cyr61	MDA-MB-231 BC cells	
	Secretable Cav-1 in CM augmented metastatic phenotype in low passage Cav-1 cutlures	LNCaP prostate cancer cells	
Estrogen signaling	Cav-1 depletion augments oncogenic transformation with upregulation of ER	MCF10A human mammary epithelial cells	[135]
	Cav-1 P132L resulted in impaired Cav-1 oligomerization, protein misfolding and loss of tumor suppressor function	mice	[140]
HER2 signaling	Cav-1 modulates receptor endocytosis of HER2-trastuzumab complex	SKBR3 BC cells	[144]
	Cav-1 as a prognostic marker for trastuzumab-emtansine ADC	human	[132]
Triple-negative breast cancer	Cav-1 silencing enhanced radiosensitivity	MDA-MB-231 and Hs587T TNBC cells	[160]
	Stromal Cav-1 is an indicator of clinical outcome independnet of tumor epithelial Cav-1	human	[162]
	Cav-1 regulates proteosomal degradation of c-MYC in BCSCs	mice	[178]
BC metastasis	Cav-1 silencing downregulated MMP-2, -9, and -1 with an increase in E-cad	BT-474 BC cells	[87]
	Cav-1 silencing mitigated lung metastasis by regulationg ITG 3α	mice	[8]
	pY14Cav-1 is involved in Rho/ROCK-dependent migration	MDA-MB-231 BC cells	[204]
	Upregulation of Cav-1 confers anoikis resistance via inactivation of caspase-8 and activation of PI3K/Akt and MEK/ERK signaling	MCF-7, MDA-MB-231 BC cells	[212], [213]

28], substantial numbers of BC patients still develop metastatic disease. BC metastasis is a significant health challenge with unmet needs. Hence, interrogation of molecular mechanisms that regulate metastasis may aid in developing effective therapies for BC treatment. Previous reports have implicated the role of caveolae integrity in cancer cell survival, migration, and metastasis [13, 22, 33, 34]. Since caveolin is an integral part of caveolae, herein, we reviewed its putative role in BC.

Structural features of Cav-1

Caveolae were first described morphologically as specialized microdomains characterized by distinct flask-shaped invaginations of the plasma membrane, which are 50–100 nm in size [35, 36]. They are generated by a family of scaffolding proteins namely Cav [37–39], including Cav-1, caveolin-2 (Cav-2), and caveolin-3 (Cav-3) [40–43]. Whilst human Cav-1 and Cav-2 are encoded by genes present on chromosome 7q31.1, Cav-3 is located on chromosome 3p25 [44, 45]. The mRNA for Cav-1 and Cav-2 contains three exons, whereas Cav-3 contains only two exons [46]. The size of Cav monomers range between 18 and 24 kDa with Cav-3 being the smallest and Cav-1 the largest [40, 47]. Both Cav-1 and Cav-2 are relatively ubiquitously present in all tissues, however, expression of Cav-3 is limited to skeletal, smooth, and cardiac muscle [48, 49].

Functionally, caveolin is made of cytoplasmic amino- and carboxy- terminals that sandwich four functional domains, namely oligomerization domain (residues 61–101), caveolin scaffold domain (CSD, residues 82–101), transmembrane domain (TMD, residues 102–134) and caveolin membrane attachment domain (C-MAD, residues 135–150) [38, 50]. The oligomerization domain that overlaps the CSD facilitates the homo and hetero-oligomerization of Cav monomers (Fig. 1).

Indeed, Cav-1 and Cav-2 hetero-oligomerize, whereas Cav-3 undergoes homo-oligomerization or forms hetero-oligomers with Cav-1 [38, 48, 51, 52]. CSD is a critical domain that mediates the protein's interaction with various binding partners and is composed of consensus motifs with aromatic rings containing amino acids [53–55]. Protein–protein interactions between caveolins and binding partners mediated through hydrophobic

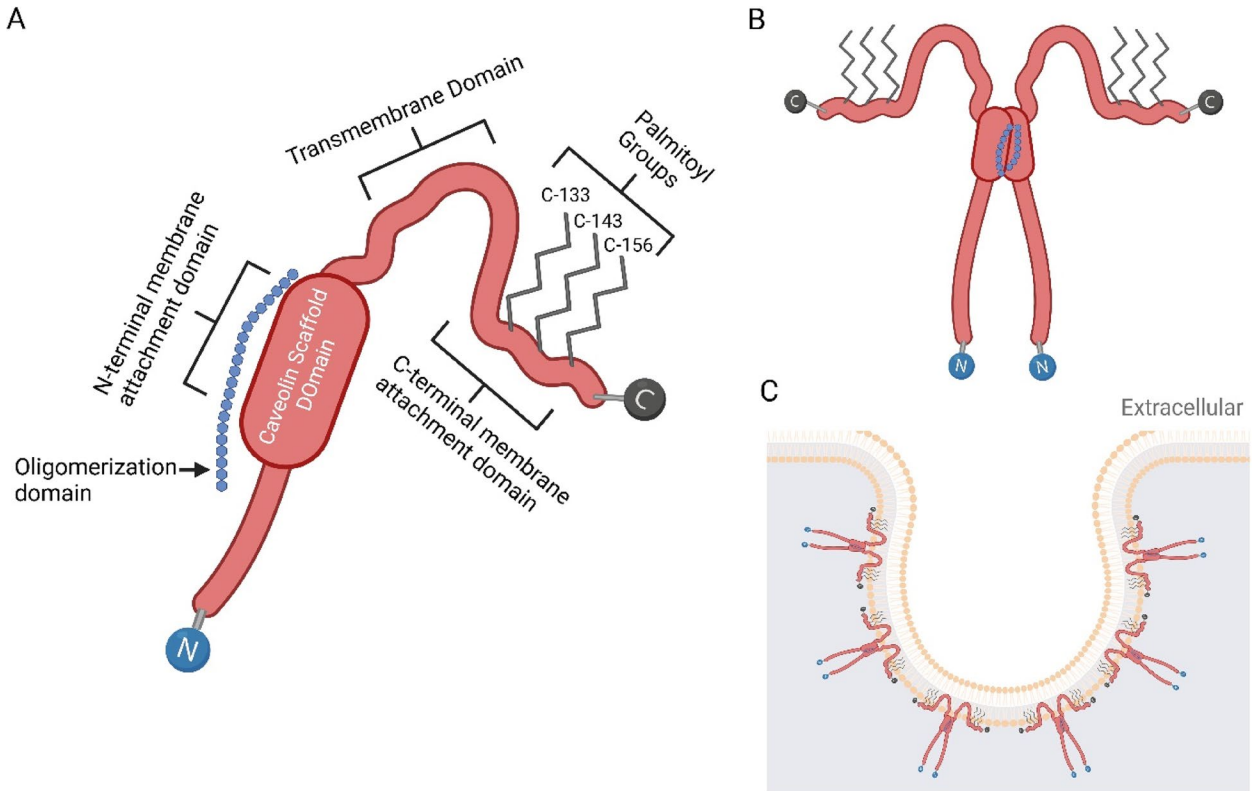

Fig. 1 Schematic representation of the domain structure of caveolin-1 and caveolae morphology. **A** Cav-1 consists of oligomerization domain (residues 61–101), caveolin scaffold domain (CSD, residues 82–101), transmembrane domain (TMD, residues 102–134) and caveolin membrane attachment domain (C-MAD, residues 135–150). Cav-1 is palmitoylated at 133, 143, and 156 sites in the C-terminal domain. **B** Oligomerization of Caveolin monomers. **C** The morphology of caveolae is represented with Cav-1 proteins forming distinct flask-shaped plasma membrane invaginations

interactions regulate the expression of these proteins in caveolae. It is through the CSD that Cav-1 interacts with partners including PKC isoforms, EGFR, eNOS, and Src-family kinases [47, 56, 57]. The presence of TMD, an α-helical hairpin loop that traverses the plasma membrane, segments N- and C-terminal of the protein to the cytoplasm [58, 59].

Although TMD is inserted in the plasma membrane, studies show that CSD and C-MAD, but not TMD, are primarily responsible for the membrane localization of caveolins. Notably, cysteine residues at positions 133, 143, and 156 are the sites where Cav undergoes palmitoylation, however, this modification was not reported to play a role in the membrane localization of Cav [60]. Spanning from the molecular intricacies of BC metastasis to the general treatment landscape, Cav-1 emerges as a focal point of interest.

Cav-1 plays a role in epithelial-mesenchymal transition (EMT), angiogenesis, and ECM degradation, thereby regulating BC metastasis. Although Cav-1 is implicated in breast primary tumorigenesis, its role in an E-cadherin-dependent transcriptional suppression of survivin through cyclooxygenase 2 (COX-2) supports a tumor suppressor function of Cav-1 [61]. Enigmatically, this dual function of Cav-1 is dependent on the cellular context and the stage of BC [62–65].

Cav-1 in cellular function

Functionally, Cav-1 orchestrates a wide array of cellular activities ranging from signal transduction and membrane trafficking to lipid transport and endocytosis through caveolae, highlighting its significance in both physiological and pathological contexts. As stated previously, the role of Cav-1 in BC is notably dualistic acting as either a tumor suppressor or promoter depending on the specific cellular environment and disease progression stage. Cav-1 thus represents a focal point for understanding cellular dynamics and the nuanced mechanisms underlying cancer pathogenesis [62–65].

Cav-1 and cell metabolism

Glycolytic shift, a hallmark of cancer enables tumor cells to primarily rely on glycolysis for energy production even in the presence of oxygen, a phenomenon termed the 'Warburg effect' [66]. The metabolic shift results in an increased production of lactate, thereby acidifying the tumor microenvironment (TME). This shift enables remodeling of ECM, angiogenesis, and invasion [67]. Notably, Cav-1 interacts with low-density lipoprotein receptor-related protein (LRP6) via its scaffolding domain to mediate Cav-1-LRP6 signaling axis. Furthermore, co-immunoprecipitation experiments have identified a cross talk between Cav-1-LRP6, and insulin-like growth factor-1 (IGF-1) receptor (IGF-1R/IR). In fact, IGF-1R/IR phosphorylation was significantly reduced in LNCaP prostate cancer cell line upon Cav-1 or LRP6 knockdown. Interestingly, phosphorylation of IGF-1R/IR was rescued upon overexpression of Cav-1 and that LRP6 silencing was enough to abrogate the observed effect. These findings suggested IGF-1R/IR phosphorylation to be downstream of Cav-1-LRP6 signaling. This signaling module induced PI3K activation, that results in an increased phosphorylation of Akt and its effector mTORC1. The phosphorylation cascade upregulates aerobic glycolysis and the expression of hexokinase 2 (HK2) and GLUT3 resulting in increased glucose uptake and lactate release, suggesting Cav-1-LRP6 module to stimulate AKT-mTORC1 signaling via activation of IGF-1R/IR in prostate cancer [68]. Interestingly, Raikar et al. [69] have reported the colocalization of phosphofructokinase (PFK) and aldolase with Cav-1 through their binding to the CSD. Consistently, the role of Cav-1 in regulating relevant glycolytic enzymes has been reported in a study that revealed a decrease in glycolytic metabolites including 3-phosphoglycerate, fructose-6-phosphate and glucose-6-phosphate in vascular endothelial cells, BAEC upon Cav-1 silencing [70]. On the contrary, overexpression of activated hypoxia inducible factor (HIF)−1α in immortalized fibroblasts (hTERT-BJ1) reduced the levels of Cav-1 with reciprocal increase in glycolysis and lactate production [71]. Since Cav-1 is a transcriptional target of HIF-1α [72], downregulation of Cav-1 coupled with an increase in the aerobic glycolysis in hTERT-BJ1 fibroblasts may be a plausible mechanism for HIF-1α mediated cancer progression.

Intriguingly, low levels of Cav-1 in invasive ductal carcinoma (IDC) induced AMPK-mediated glycolysis via transcription factor NRF2-activated manganese-dependent superoxide dismutase (MnSOD) [73]. In the same study, ectopic expression of Cav-1 in MCF-7 BC cells revealed a downregulation in NRF2 expression and MnSOD induction, and reduced aerobic glycolysis suggesting low Cav-1 expression may be linked to enhanced aerobic glycolysis in these cells [73].

Hence, the role of Cav-1 in glycolysis is context-dependent with a limited understanding that needs further interrogation. In addition, the loss of Cav-1 in mouse embryonic fibroblasts (MEFs) resulted in the accumulation of cholesterol in mitochondrial membranes, coupled with elevated ROS levels [74]. This report provides a putative link between Cav-1 and cholesterol flux in the mitochondrial membrane, suggesting a tissue-specific loss of Cav-1 to be an effector of dysregulated mitochondrial activity. Taken together, these reports strongly suggest a role for Cav-1 in cellular bioenergetics in cancer.

Role of Cav-1 in autophagic tumor stroma

Within the tumor stromal compartment, tumor cells induce oxidative stress (OS) in the surrounding stromal cells. In support of this, cocultures of MCF-7 BC cells and HTERT-BJ1 immortalized fibroblasts demonstrated an oxidative storm as reflected by an increased ROS production in the adjacent fibroblasts. Thus, increased OS compromised mitochondrial function, ROS production, and mitochondrial autophagy in stromal fibroblasts leading to autophagy through the activation of HIF-1α and NF-kβ in the fibroblasts [71, 75–77] Autophagy in the stromal fibroblasts results in enhanced aerobic glycolysis, thereby, providing nutrients including lactate, pyruvate, and ketones, to fuel the tumor epithelial cells, so-called 'reverse Warburg effect' [78]. Induction of autophagy and OS by tumor epithelial cells results in depletion of Cav-1 in stromal fibroblasts [75, 76]. Several studies have reported the downregulation of Cav-1 in cancer-associated fibroblasts (CAFs) derived from breast tumors [79–81]. Proteomic analysis of Cav-1 deficient fibroblasts revealed a comprehensive list of gene products that were upregulated to enable myofibroblast phenotype [82]. In relevance, a significant upregulation in the expression of collagen VI (COL6A1, COL6A2) in Cav-1 depleted stromal fibroblast was indicative of lymph node metastasis in BC patients [83]. Consistently, deletion of collagen VI gene in the MMTV-PMT mouse model reduced the formation of mammary dysplastic lesions [84, 85], highlighting the loss of Cav-1 in stromal fibroblasts to have a lethal effect within the TME. Apparently, Cav-1 depleted fibroblasts increased the tumor volume and mass by ~ fourfold in mouse xenograft experiments that involved MDA-MB-231 cells [82].. Interestingly, treatment with a cell-permeable Cav-1 peptide inhibited the growth of CAFs that suggested Cav-1's antiproliferative effect on CAFs [79].

Studies have shown that Cav-1 regulates autophagy [86, 87], however, its role is ambiguous. For instance, in hepatocellular carcinoma (HCC), Cav-1 is inversely regulated autophagy [86], whilst it has a direct link in ER^+ BC cell line [87]. In general, microtubule-associated protein 1 light chain 3 (LC3), ATG 12/5, and Beclin-1 are regarded as autophagy markers. During the process of autophagy, LC3-I is converted to LC3-II and the ratio of LC3-II/LC3-I is an indicator of autophagy [88]. Similarly, ATG12/ATG5 complex acts like a ubiquitin-conjugation system to target autophagosome vesicles [89], and Beclin-1 is involved in autophagosome formation [90]. Interaction of Cav-1 with LC3 via the CSD [91], and in complex with ATG12/5 [92] segregates the autophagic markers thereby preventing the autophagosome formation. In HCC, depletion of Cav-1 was linked to an upregulation of LC3, ATG12/5, and Beclin-1 to facilitate the onset of autophagy [86]. On the contrary, BT-474 ER^+ BC cells treated with estradiol resulted in an upregulated of Cav-1, HMGB1,LC3-II, ATG12/5, andBECLIN-1 [93]. In this context, Cav-1 silencing downregulated HMGB1, LC3-II, ATG12/5, but not Beclin-1. Likewise, depletion of HMGB1 resulted in reduced expression of LC3-II, ATG12/5, and Beclin-1, however, expression of Cav-1 was not altered. Hence, the authors implicated the role of HMGB1 in estradiol/Cav-1-induced LC3-autophagy in BT-474 BC cells [93].

It should be noted that the prognostic value of depleted stromal Cav-1 expression was independent of pre-existing epithelial markers of luminal BC such as ER, PR, and HER2 [78]. Thus, Cav-1 retains the prognostic value even in TNBCs. Low stromal Cav-1 can be a strong indicator of the progression from pre-invasive lesions like ductal carcinoma in situ (DCIS) to invasive BC [94].. In accordance, Qian et al. [80] have linked high tumor Cav-1 expression and depleted stromal Cav-1 levels to worse clinical outcomes in BC patients. Overall, these studies highlight a role for Cav-1 in autophagy that needs further investigation.

Cav-1 in apoptosis and cellular senescence

Although several studies have implicated the role of Cav-1 in regulating apoptosis [95–99], its role remains controversial. Whilst caveolae contain sphingomyelin-cholesterol enriched microdomains, various cellular stresses including proapoptotic signals alter this lipid matrix resulting in the hydrolysis of sphingomyelin to generate ceramide. It would appear that Cav-1 may regulate growth factor receptor signaling through PI3K. In agreement, Cav-1 was reported to bind to a consensus motif of PI3K to modulate receptor-mediated protein kinase activity.

Based on previous studies [100, 101] that described ceramide-mediated inhibition of Akt activation independent of PI3K activity, Zundel et al. [99] have reported phosphorylation of Cav-1 to enable the observed inhibition of Akt activation. Shahjahan et al. [95] have identified the phosphorylation of Cav-1 on tyrosine residue, Y14Cav-1 to modulate paclitaxel-induced apoptosis in MCF-7 BC cells. In this study, upon transfection of MCF-7 cells with wtCav-1, but not the phosphorylation-deficient mutant, Y14F induced sensitivity to paclitaxel. This was due to an increased mitochondrial permeability of wtCav-1 over the MCF-7/Y14F cells. Inactivation of anti-apoptotic function of Bcl-2 via its phosphorylation by paclitaxel followed by G2/M cell cycle arrest lead to apoptosis in these cells [95].

On the contrary, Badana et al. [97] have reported downregulation of Cav-1 in MDA-MB-231 and MDA-MB-468 cells upon induction of apoptosis with

methyl-β-cyclodextrin (MβCD), a cholesterol depleting agent. Downregulation of Cav-1, LRP6, β-catenin, survivin, caspase-3, Bcl-2, and Bax were attributed to the disruption of lipid rafts upon treatment with MβCD. Consistently, the clonogenic potential and expression of Cav-1 in these cells were enhanced upon cholesterol supplementation [97].

Cellular senescence is a complex biological process that serves as a mechanism for tumor suppression by arresting cell cycle [19, 102, 103]. Interestingly, increased expression of Cav-1 inhibited epidermal growth factor (EGF) stimulation of senescent human diploid fibroblasts [104, 105]. In agreement, depletion of Cav-1 resumed DNA replication and cell cycle progression coupled with the downregulation of senescence markers including p53 and p21 [106]. Bartholomew et al. [107] have shown that Cav-1 sequesters Mdm2 upon OS in human fibroblasts. Sequestration of Mdm2 leads to the stabilization of p53 and subsequent upregulation of $p21^{WAF1/Cip1}$ to augment cellular senescence. Moreover, OS-induced transcriptional upregulation of $p21^{WAF1/Cip1}$ was not reported in Cav-1 null MEFs, supporting the role of Cav-1 in the onset of cellular senescence in MEFs [107]. In another study, Cav-1 was reported to sequester nuclear erythroid 2 p45-related factor-2 (Nrf2) in the plasma membrane after OS, thereby limiting the translocation of Nrf2 to the nucleus and inhibiting the transcription of antioxidant response element (ARE) [108]. Consistently, mutant Nrf2 that lacks the ability to interact with Cav-1 translocated to the nucleus to hyperactivate AREs.

Subsequently, OS-induced $p53/p21^{WAF1/Cip1}$-mediated cellular senescence in human fibroblasts was inhibited [108]. Similarly, Cav-1 through its CSD interacts with Cav-1 binding domain of Sirtuin 1 (Sirt1) [109]. Following OS, Sirt1 is sequestered in the plasma membrane followed by its inactivation upon interaction with Cav-1. Subsequently, OS promotes acetylation of p53 and onset of premature senescence in human fibroblasts [109]. Furthermore, expression of Cav-1 in Cav-1-null fibroblasts induced p53-mediated senescence. Collectively, these studies implicate the role of Cav-1 in cellular senescenence.

Cav-1 and cell cycle progression

The role of Cav-1 in regulating cell cycle progression has been extensively studied [110–113]. In general, Cav-1 is a transcriptional repressor of cyclin D1 [114], a regulator of cyclin-CDK complex that facilitates G to S phase transition. Consistently, Galbaiti et al. [110] have demonstrated cell cycle arrest in the G_0/G_1 phase upon transient transfection of NIH 3T3 cells with Cav-1, coupled with a decrease in the percentage of cells in the S phase. Consistently, downregulation of Cav-1 in NIH 3T3 cells revealed transition of cells from G_0/G_1 phase with increased population of cells in the S phase. Such an effect was mediated via p53 activity. Notably, Cav-1 transgenic mouse embryonic fibroblasts (MEFs) revealed a significantly higher p53 activity resulting in the induction of $p21^{WAF1/Cip1}$ as compared to the control MEFs [110]. The authors predicted that the observed cell cycle arrest in Cav-1 MEFs was mediated via p53/p21 pathway. In a different study, Hayashi et al. [115] have shown oncogenic induction in NIH 3T3 cells upon expression of Cav-1 P132L mutant. The observed transformation was speculated to be due to the hyperactivation of p42/44 MAP kinase signaling. In agreement, Galbaiti et al. [113] demonstrated activation of p42/44 signaling in NIH 3T3 cells when Cav-1 was depleted, leading to anchorage-independent growth, oncogenic ability, and tumor formation in immunodeficient mice. Interestingly, Cav-1 P132L mutant exerted oncogenic activity similar to antisense Cav-1 depletion. Notably, transfection of Cav-1 to normal levels reversed this oncogenic transformation [113]. Conclusively, these studies implicate a direct role of Cav-1 in the regulation of cell cycle progression.

Cav-1 and immune regulation

Presence of caveolae or caveolin −1 in immune cells has been a contentious topic, however, studies have shown that they are present in all types of immune cells including murine macrophages and mast cells [116–118], bovine macrophages and dendritic cells [119, 120], and human dendritic cells [119]. Notably, activation state of the cell remains a crucial indicator of the expression and distribution of caveolae and Cav-1. For instance, transfected human T cells [121] or activated T-cell leukemia lines [122] expressed Cav-1, whilst human and murine lymphocyte cell lines lacked the presence of Cav-1 [123]. Interestingly, bovine $CD4^+$, $CD8^+$, and $CD21^+$ IgM lymphocytes upon staining revealed the presence of Cav-1 to be localized in the perinuclear region [120], meanwhile, the protein was detected at the cell surface of human $CD21^+$ and $CD26^+$ lymphocytes [124]. Based on these observations, it can be speculated that the expression pattern of Cav-1 may depend on the cells in context. Consistently, upon staining of rat resident macrophages, caveolae appeared to be sparse with Cav-2 predominantly localized within the vesicles of the Golgi apparatus. Upon stimulation with complete Freund's adjuvant, dense caveolae with caveolin staining throughout the cell was detected [117, 118, 125]. In agreement, lipopolysaccharide stimulation of mouse macrophages induced an upregulation of Cav-1 expression [126]. Collectively, these reports suggest that the expression pattern of Cav-1 is strongly related to the activation state of the cells and indirectly suggest a role for Cav-1 in immune regulation.

Studies have implicated the role of Cav-1 in various aspects of immune regulation, including inflammation [127, 128], pathogen entry [129], and T-cell activation [128]. Two different studies have identified the role of Cav-1 in T-cell activation and subsequent antigen-specific immune response in rheumatoid arthritis (RA) [127, 128]. Ohnuma et al. [128] have demonstrated binding of CD26/dipeptidyl peptidase IV (DPPIV) to CSD of Cav-1 to induce antigen-specific T-cell activation in response to the tetanus toxoid (TT). In this study, it was reported that CD26, a T-cell costimulatory molecule with DPPIV activity, interacts with CSD of Cav-1 and that residues 201–211 of CD26 along with catalytic serine site at position 630 contribute to binding to Cav-1. Following this, Cav-1 on the TT-loaded monocytes undergoes phosphorylation resulting in the activation of NF- κB, and upregulation of CD86. This in turn enables an interaction with CD28 on T-cells resulting in TT-specific T-cell activation in RA [128].

A study by Mirza et al. [130] highlighted the significance of Cav-1 in the regulation of innate immunity via endothelial nitric oxide synthase (eNOS) in response to LPS stimulation of lung endothelial cells. Herein, upon LPS challenge, the de-inhibition of eNOS resulted in a decreased levels of pro-inflammatory molecules and NF-κB activation in Cav-1$^{-/-}$ mice as compared to the wild-type. In the Cav-1$^{-/-}$ deficient mice, the protective effect was attributed to an increased nitration coupled with decreased kinase activity of interleukin (IL)−1R-associated kinase (IRAK) 4 upon eNOS activation. In general, LPS binding of Toll-like receptor, (TLR)−4 recruits a complex signaling cascade that involves MyD88, an adaptor molecule-dependent phosphorylation of IRAK4 coupled with the activation of transforming growth factor β activated kinase (TAK1) to induce NF-κB. Interestingly, upon LPS activation, eNOS dissociates from Cav-1 to synthesize NO [131], thereby mitigating effects of proinflammatory cytokines such as tumor necrosis factor (TNF)-α, macrophage inflammatory protein 1 (MIP 1), and intercellular adhesion molecule (ICAM)−1. In summary, the role of Cav-1 was implicated in the modulation of innate immunity and inflammation of lung endothelial cells upon LPS activation via eNOS activity [130].

In a different study, Cav-1 was shown to modulate the inflammatory response during gram-negative bacterial infection [129]. For instance, using coimmunoprecipitation and computational models, Cav-1 was reported to colocalize with toll-like receptor (TLR)−4. Upon deletion of Cav-1, outer membrane vesicle (OMV)-induced TLR response and proinflammatory cytokine release including TNF-α and IL-1β was upregulated suggesting a putative role for Cav-1 in OMV-induced TLR response [129]. Taken together, these reports strongly support the role of Cav-1 in immune regulation. Despite its role in immune regulation, there is a caveat in the existing knowledge which concerns the implication of Cav-1 in BC.

Collectively, these findings highlight the role of Cav-1 in multiple pathways beyond oncogenic signaling that regulate cellular bioenergetics, autophagy, apoptosis, senescence, cell cycle progression, and immune regulation that needs further investigation. Although Cav-1 seems to play a vital role in several biological processes, its role in breast carcinogenesis is not fully understood. Moreover, BC is a heterogeneous disease with several subtypes each regulated by specific pathways [24, 25], likewise, the role of Cav-1 in such diverse systems varies widely. In the following section, the role of Cav-1 in BC subtypes is discussed.

Cav-1 and breast carcinogenesis

The current literature on the role of Cav-1 in BC progression is somewhat disjointed. Nor is it clear whether it acts as an oncogenic promoter or a suppressor protein. Nevertheless, the differential expression of Cav-1 in BC subtypes with varied genetic backgrounds may justify the diversified role of Cav-1 in BC. For instance, Chung et al. [132] have demonstrated differential expression of Cav-1 protein in various BC cell lines, the highest expression in MDA-MB-231 TNBC cells, whilst HER2^{+} metastatic SKBR3 cells with moderate, and trastuzumab-sensitive BT-474 cells with the lowest levels of Cav-1 expression respectively. In support of this, two contradictory investigations uncovered the dual of Cav-1 in BC metastasis [8, 133]. First, using an orthotopic murine model of TNBC, Sloan et al. [133] demonstrated a decrease in the metastatic spread to the lung and bone upon exogenous expression of Cav-1 in highly metastatic 4T1.2 cells.

Next, findings from our lab have demonstrated decreased lung metastasis in mice induced with 4T1 murine TNBC cells upon Cav-1 KO via integrin α3 dysregulation [8]. A plausible explanation for the dual role of Cav-1 is the context-specific function, in this case, 4T1.2 cells have proclivity for bone metastasis as compared to the 4T1 cells that metastasize to the lungs.

Cav-1 in estrogen signaling

A study by Lee et al. [111] provided the first functional evidence that Cav-1 functions as a tumor suppressor. In this study, re-expression of Cav-1 in the T47D human luminal BC cells resulted in decreased cell proliferation and subsequent reduction of anchorage-independent growth [111]. Consistently, Hino et al. [134] demonstrated reduced cell growth and viability upon expression of Cav-1 in MCF-7 cells. Furthermore, Zou et al. [135] generated two clones, ST1 and ST3 of MCF10A human

mammary epithelial cells with potential for transformation. Upon further analysis, Cav-1 levels were depleted with simultaneous upregulation of ERα in both these clones, suggesting an inhibitory role of Cav-1 in the transformation of MCF10A [135]. Studies focused on the relation between Cav-1 and ER^+ BC determined Cav-1 to play a tumor suppressor role [136–138]. Caveolin-1 is a negative regulator of co-activator of AP-1 and ER (CAPER), a nuclear transcriptional co-activator of ERα and JUN/AP1 [136, 138].

It is noteworthy that Src-mediated phosphorylation of Cav-1 at tyrosine residue 14, Y14Cav-1, in primary cultures of HLMVECs human lung microvascular endothelial cells and RLMVECs rat lung microvascular endothelial cells resulted in the dissociation of Cav-1 oligomers [139]. Furthermore, a phosphomimetic Y14DCav-1 mutant confirmed the destabilization of Cav-1 oligomers. This study speculated that pY14 event accommodates cargo and allows the dissociation of Y14DCav-1 from the plasma membrane [139].

In a different study, inactivating mutation involving proline-to-leucine substitution, Cav-1 P132L, resulted in impaired Cav-1 oligomerization, protein misfolding, and retention within the Golgi complex [140]. It may be speculated that Cav-1 P132L mutant renders the protein functionally inactive, thereby losing its tumor suppressor activity in ER^+ BCs. Of note, Cav-1 P132L mutation was detected in 19% of ERα-positive BC patients, thus linking the Cav-1 P132L mutation to ER^+ BC [141]. Since P132L is detected in ERα-positive BC patients, the association between Cav-1 carrying the point mutation P132L and tamoxifen resistance is relatable as ~ 50% of ER^+ BC cases become insensitive to tamoxifen treatment [142].

Cav-1 in HER2 signaling

Park et al. [143] and colleagues reported an association between Cav-1 and HER2 in BC. They have demonstrated a reduction in Cav-1 expression in 43.1% of 130 cases of invasive ductal carcinoma, whilst an inverse correlation was significant between Cav-1 and EGFR and HER2 in these samples [143]. Hence, in the absence of HER2, the oncogenic function of Cav-1 is speculated through EGFR and MAPK signaling. Cav-1 was shown to modulate receptor endocytosis of HER2-trastuzumab complex in $HER2^+$ cancers [144]. Pereira et al. [145] reported an increased plasma membrane half-life of HER2 and availability leading to an enhanced sensitivity of $HER2^+$ BC to trastuzumab therapy upon depletion of Cav-1. Consistently, a different study reported Cav-1 as a prognostic marker for Trastuzumab-Emtansine (T-DM1) antibody–drug conjugate (ADC) treatment in BC patients [132].

Interestingly, a study conducted by Chung et al. [132] reported an increased Cav-1 expression in 68% of BC specimens (out of 32). Furthermore, 72.7% (8/11) of these patients were $HER2^+$. This study investigated the effect of Cav-1 on the chemosensitivity of $HER2^+$ BC cells to T-DM1. The findings revealed colocalization of T-DM1 and Cav-1 in SKBR3 luminal BC cells with increased chemosensitivity as compared to BT-474 TNBC cells. It is noteworthy that SKBR3 cells express moderate levels of Cav-1 in contrast to low levels in BT-474 cells [132]. This suggests that Cav-1 expression might be a determinant of the observed chemosensitivity of $HER2^+$ cancers to T-DM1. Upon transfection of BT-474 cells with GFP-tagged Cav-1, these cells demonstrated enhanced drug responsiveness to T-DM1 in contrast to the Cav-1-silenced SKBR3 cells [132]. In conclusion, the role of Cav-1 in T-DM1 mediated cytotoxicity in $HER2^+$ BC may support its use as an effective predictor of disease prognosis.

Cav-1 in triple negative breast cancer

TNBC is an aggressive form of BC that accounts for approximately 15–20% of BC morbidity [146–149] with a propensity for metastasis accompanied by the worst prognosis. Unfortunately, lack of efficacious targeted therapies pose a significant challenge in the treatment of this disease [28]. Despite these challenges, only limited therapeutic options, such as neoadjuvant chemotherapy (NACT) including taxanes, platinum compounds and anthracyclines are effective early on, yet a high disease relapse rate renders the treatment ineffective [27, 146–148, 150–154].

Previous reports [155–158] have demonstrated an upregulation of Cav-1 in basal-like TNBC cells. Williams et al. [159] indicated a poor prognostic role for Cav-1 in $HER2^-$ BC upon paclitaxel treatment. Interestingly, enhanced radiosensitivity was reported of MDA-MB-231 and Hs587T cells upon Cav-1 silencing [160]. However, Hs587T cells required a relatively higher single dose radiation of 8 Gy as compared to 6 Gy radiation to induce comparative extent of apoptosis in MDA-MB-231 cells [160], implicating a role for Cav-1 in radiosensitization of basal-like TNBC cells.

Several studies have suggested that a more favorable prognosis for patients with TNBC depends on the compartment-specific expression of Cav-1 within the TME [161–167]. For instance, Witkiewicz et al. [162] reported median survival rates of 25.7 months for TNBC patients (cohort size of 85) with no stromal Cav-1 levels. Similarly, the median survival rate was 33.5 months for TNBC patients with moderate levels of Cav-1, however, > 50% of TNBC patients with high levels of stromal Cav-1 survived during a 12-year of follow-up. This study suggested stromal Cav-1 as an indicator of clinical outcome, however, presence of tumor epithelial Cav-1 had no prognostic value [162].

Consistently, findings by Koo et al. [161] implicated stromal Cav-1 expression in 91.7% (132 out of 144) of Korean TNBC cases, whilst only 5.6% of these cases were positive for epithelial Cav-1 expression. Another study by Yeong et al. [168] was in agreement with the above findings where 14.4% of a total of 699 cases of TNBC were positive for stromal Cav-1 expression. Collectively, these reports can be used to reach a broader consensus that the expression of stromal Cav-1 and not the tumor epithelial Cav-1 has favorable prognostic significance.

Accumulating evidence suggests that highly aggressive TNBCs have a substantially high percentage of BC stem-like cells (BCSCs) [169–171] and Cav-1 has been implicated in regulating the BCSC metabolism [73, 172–177]. Interestingly, Wang et al. [178] have demonstrated that the downregulation of Cav-1 resulted in increased aerobic glycolysis in BCSCs. Indeed, depletion of Cav-1 was linked to enhanced mammary ductal hyperplasia and tumor formation in transgenic mice [178]. Furthermore, the study highlighted a putative role for Cav-1 in Von Hippel-Lindau (VHL)-mediated proteasomal degradation of c-MYC, thus inhibiting the metabolic switch observed in BCSCs [178]. Taken together, these studies verify Cav-1 as a promising prognostic biomarker for TNBC, however, due to its context-dependent role, its use merits further study.

Studies have reported loss of stromal Cav-1 in human BC associated fibroblasts [79–81, 83], nevertheless, absence of Cav-1 in breast tumor stroma in vivo remains enigmatic. Witkiewicz et al. [179] reported expression of stromal Cav-1 to be a useful tool to categorize BC patients into low- and high-risk group with regard to tumor lymph node metastasis (TNM). Albeit, the presence or absence of Cav-1 may not be correlated with ER, HER2, and TNBC subtypes. For instance, out of 125 BC patient samples, absence of stromal Cav-1 was reported in 47, whilst 78 samples had detectable levels of Cav-1 in the tumor stroma [179]. 76% of ER^+ patients had stromal Cav-1 present, as compared to ER^- patients at 60%. In this case, a correlation between stromal Cav-1 and ER status suggested a trend yet was not statistically significant ($p=0.097$). Notably, there was no significant association between HER2 expression and stromal Cav-1 status ($p=0.341$). Likewise, presence or absence of stromal Cav-1 was independent of the triple-negative status ($p=0.0593$). Importantly, 49% of the patients with absence of stromal Cav-1 were positive for lymphovascular invasion (LVI), as compared to 30% of patients with presence of stromal Cav-1 suggesting a significant correlation ($p=0.048$) between the absence of stromal Cav-1 and LVI, a strong predictor of metastasis [179]. In conclusion, whilst the presence or absence of stromal Cav-1 is not significantly correlated with ER, HER2, or TNBC status, its absence is strongly correlated with BC metastasis, regardless of the BC subtypes.

Role of Cav-1 in metastatic BC

As previously mentioned, metastasis is the primary cause of death among cancer patients [4–7]. Metastasis is a complex process that entails a series of sequential and interrelated stages resulting in the formation of secondary tumors at distant sites beyond the primary site where the tumor initiated. Several studies have implied a role for Cav-1 in the metastatic cascade [8, 21, 23]. This process involves detachment of cancer cells from the primary tumor site, entry into the blood or lymphatic systems (intravasation), survival in the bloodstream, extravasation, adaptation to the foreign microenvironment, and successful proliferation and colonization at distant sites. We discuss here a promising role for Cav-1 in the metastatic cascade of BC.

Cav-1 and ECM interactions

One of the prerequisites in the onset of metastasis involves the EMT of tumor cells and dissolution of ECM to enable tumor cell detachment from the primary site and subsequent intravasation.

In this aspect, matrix metalloproteinases (MMPs) play a significant role in the proteolytic degradation of ECM proteins [180]. Interestingly, the knockdown of Cav-1 in BT-474 BC cells resulted in the downregulation of MMP-2, −9, and −1 with simultaneous upregulation of E-cadherin [87] indicating a mesenchymal to epithelial transition (MET). As previously mentioned, loss of stromal Cav-1 is linked to metastasis [181–183]. Consistently, Dees et al. [184] have demonstrated an upregulation of the transcription factor, STAT5a coupled with an elevated MMP-9 expression within the DCIS-like lesions in Cav-1 KO mice treated with estrogen. Further studies by Al-Ansari et al. [185] provided conclusive evidence that treatment of CAFs with caffeine upregulated the stromal Cav-1 leading to reduced MMP secretion. Collectively, these studies support the regulatory role of Cav-1 in ECM degradation in BC via MMP secretion.

Several studies in melanoma and colon cancer have postulated a role for Cav-1 in regulating the ECM interactions via E-cadherins [186–189]. For example, HT29 human colon cancer cells expressing E-cadherin promoted the sequestration of β-catenin to the plasma membrane which was mediated by Cav-1 [186] to preclude T-cell factor (Tcf)/Lef-dependent transcription of survivin and COX-2 genes thereby inhibiting tumor progression and inflammation [186, 187]. Parallel studies in B16F10 murine melanoma cells expressing low levels of E-cadherin and Cav-1 resulted in reduced tumor formation and mitigated lung metastasis upon ectopic

expression of Cav-1 [188]. Hence, it can be argued that the interaction between E-cadherin and Cav-1 regulates ECM interactions, importantly, the later supported the role of E-cadherin in determining the function of Cav-1 to be a tumor suppressor or tumor metastatic in melanoma cells.

Role of Cav-1 in cell migration and invasion

Cav-1 undergoes posttranslational modifications including phosphorylation on tyrosine-14, pY14Cav-1 [190, 191]. Interestingly, pY14Cav-1 is reported to activate c-*Src* through inactivation of C-terminal Src kinase (CSK) by Cav-1, thereby resulting in increased cell migration [16, 192–195]. Lee et al. [191] have demonstrated the binding of pY14Cav-1 to Grb7, an SH2 domain-containing protein in NIH 3T3 fibroblasts. Grb7 may function as a potential linker between Cav-1 and other SH2 binding proteins as well as tyrosine kinases such as EGFR [53], focal adhesion kinase (FAK) [196], and integrin subunits [197, 198].

Recently, we have reported that integrin α3 is differentially regulated upon Cav-1 KO in 4T1 murine TNBC cells [8]. Furthermore, Lee et al. [191] have demonstrated cell migration and anchorage-independent growth upon ectopic expression of c-Src, Grb7, Cav-1 (WT) in 293 T cells. Intriguingly, co-transfection with phosphonull mutant, Y14ACav-1, alone or in combination with c-Src, Grb7 abrogated cell migration and growth suggesting pY14Cav-1 to play a crucial role in the observed effects [191].

Diaz-Valvidia et.al [199]. reported an interaction of Cav-1 with protein tyrosine phosphatase PTPN14 in B16F10 murine melanoma cells expressing E-cadherin. In the absence of E-cadherin, such an association was not observed. Nevertheless, overexpression of PTPN14 dephosphorylated Y14Cav-1 that suggested the later event to be independent of E-cadherin [199]. Consistently, overexpression of PTPN14 reduced the phosphorylation of Y14Cav-1 in metastatic MDA-MB-231 BC cells, thereby inhibiting cell migration and invasion [199]. Hence, it can be argued that PTPN14 acts as a tumor suppressor in modulating the phosphorylation-dependent functions of Y14Cav-1.

The ability of cancer cells to migrate is a key determinant of cancer metastasis. In this regard, Diaz et al. [200] have demonstrated an increase in Rab5 activation, an important regulator of endosome biogenesis and trafficking, in the presence of Cav-1 in MDA-MB-231 cells. Ectopic expression of p85α (RAB5-GAP) in MDA-MB-231 cells following the depletion of Cav-1 resulted in reduced cell migration [200]. This led to an assumption that the presence of Cav-1 may sequester p85α in a complex thereby stimulating Rab5-GTP-induced cell migration in MDA-MB-231 cells.

In a different study, Goetz et al. [195] reported Mgat5/Gal-3 activation of FAK and FA turnover to be mediated via pY14Cav-1 in mammary carcinoma cells. Indeed, the observed FA dynamics and propulsive activity were regulated by Cav-1, but not phosphonull mutant Y14FCav-1, suggesting a role for Cav-1 in the migration and invasion of BC cells [195].

A comprehensive cDNA microarray analysis of inflammatory BC (IBC) cell lines including SUM-190 and SUM-149; and human tissue samples of IBC revealed hypomethylation of CpG islands in the promoter sequence within Cav-1 gene as compared to the non-IBC MCF10A and SUM-102 [201].

Since hypomethylation of CpG dinucleotides results in overexpression of the gene [202], it may be obvious that hypomethylation of Cav-1 promoter may lead to an upregulated gene expression in IBC cell lines. Based on the findings that RhoC is often upregulated in IBC phenotype [203] it may therefore be possible that the RhoC GTPase activation is regulated by the overexpression of Cav-1, however, the functional relevance of this relationship is yet to be established.

In a different study, Rho/ROCK-dependent migration, and invasion of MDA-MB-231 involved pY14Cav-1 [204] suggesting a role for Cav-1 in tumor metastasis through the regulation of FA turnover. The role of Cav-1 in BC metastasis extends beyond Rho/ROCK-dependent migration to encompass mitochondrial dynamics [20]. In general, chemotherapeutic agents increase the levels of mitochondrial ROS (mtROS) thereby driving apoptosis in cancer cells. Mitophagy is a type of autophagy that eliminates mtROS to enable cancer cell survival [205–208]. Interestingly, pY14Cav-1 level inhibits the interaction of Mitofusin 2 (Mfn2), a mitochondrial fusion protein, with PINKI/Parkin by sequestering Mfn2 to the plasma membrane [20]. Thus, pY14Cav-1 negatively regulates the formation of Mfn2/PINKI/Parvin complex resulting in the resistance of TNBC cells to doxorubicin via inhibition of mitophagy [20]. Overall, pY14Cav-1 was shown to promote BC cell migration via Rho GTPase activity [203, 204], besides inhibiting mitophagy via limiting the access of Mfn2 to mitochondria. Therefore, it may be possible that by regulating the levels of pY14Cav-1 in BC cells the chemotherapeutic efficacy may be augmented.

Cav-1 and anoikis resistance

Detachment from the surrounding ECM triggers anoikis, a type of programmed cell death, to ensure that the cells do not survive in inappropriate locations. However, metastatic cancer cells acquire the ability to resist anoikis which allows these cells to invade distant organs

[209–214]. In relevance, metastatic MDA-MB-231 BC cells upregulate the expression of Cav-1 to confer anoikis resistance by inactivating caspase-8 with simultaneous activation of cell survival pathways including PI3K/Akt and MEK/ERK [212, 213]. Also, metastatic tumor cells are encountered with a biomechanical challenge of fluid shear stress within the circulatory system [215, 216]. Chen et al. [211] have demonstrated an induction of ROS and •NO in MDA-MB-231 cells upon exposure to low shear stress of 2dyn/cm [2]. These reactive intermediates stabilized Cav-1 by preventing its ubiquitination and proteasomal degradation, thus enhancing the resistance of these cells to anoikis [211].

Cav-1 and EVs

Besides, pY14Cav-1, a second major phosphorylation site for Cav-1 is at serine-80, S80 [217, 218]. In this study, using site-directed mutation in fibroblast cells including COS7 and 293 T, authors demonstrated that S80 to glutamate substitution, S80E (phosphomimetic) converted Cav-1 to secretary protein. Thus, the secretary Cav-1 had transformation potential with a similar effect as loss of Cav-1 [217]. Furthermore, a phosphonull mutant at position 80 converting serine to alanine, S80A resulted in the loss of the secretory Cav-1, suggesting that pS80Cav-1 is an essential step for its ER-mediated secretion [217].

Campos et al. [219] speculated that Cav-1 may be transported in extracellular vesicles (EVs) to facilitate PMN formation by delivery of adhesion molecules. In this study, the authors reported that the EVs released from MDA-MB-231 BC cells contained protein cargo including tenascin and cysteine-rich angiogenic inducer 61 (Cyr61) that modulated the invasive potential of the recipient cells and that the presence of Cav-1 in these EVs determined the composition of the protein cargo [219]. Consistently, Wang et al. [21] demonstrated that an increased level of Cav-1 in tumor-derived exosomes induced BC metastasis of noninvasive MCF-7 as well as highly aggressive MDA-MB-231 cells. Furthermore, Cav-1 in BC-derived exosomes regulates the expression of PMN markers in lung epithelial cells along with the secretion of tenascin-C in lung fibroblasts. In addition, the exosomal-derived Cav-1 also facilitated M2 polarization of lung macrophages via inhibition of PTEN/CCL2/VEGF-A pathway [21]..

Parallel studies have detected a significantly higher level of Cav-1 in serum of patients with advanced prostate cancer [220, 221]. Consistently, conditioned medium (CM) from human prostate cancer, LNCaP with high passage with secretable Cav-1, (LNCaPCav-1) augmented the viability and metastatic characteristics of low passage, Cav-1 negative LNCaP cells [220].

Recent evidence has linked an increased plasma concentration of Cav-1 and EV generation to be associated with reduced expression of Cav-1 in human lung endothelial cells (EC) with arterial hypertension [222]. In this study, it was shown that depletion of Cav-1 in EC may be due to its segregation in the EV, suggesting a role for Cav-1 as a plasma biomarker of endothelial cell injury.

Another study by Lee et al. [223] has highlighted the role of Cav-1 in cargo sorting within EVs. The findings of this study revealed a putative interaction between Cav-1 and heterogenous nuclear RNA binding protein A2B1 (hnRNPA2B1), an RNA-binding protein. Upon OS, pY14Cav-1 undergoes conformational change to augment an interaction with arginine-glycine-glycine (RGG) domain of hnRNPA2B1 [223]. Furthermore, tyrosine Y97 and phenylalanine F99 in the CSD function as docking sites to enable Cav-1/hnRNPA2B1 interaction [223]. Although, Ostermyer et al. [224] reported Y97, tryptophan W98, F99, and Y100 to be responsible for Cav-1 trafficking to the plasma membrane, there is lack of evidence to support the interaction of W98, and Y100 residues with hnRNPA2B1. Nevertheless, upon OS, hnRNPA2B1 undergoes O-GlcNAcylation of serine S73 and serine S90 in the RGG domain, a post translational modification that plays an important role in hnRNPA2B1–miRNA interactions [223]. In a different study, Kou et al. [225] have demonstrated the interaction of Cav-1 with Fas and SNAP25, and tyrosine phosphatase Fap-1 with Fas and Cav-1. This interaction resulted in the generation of EVs containing SNAP25/VAMP5-associated interleukin 1 receptor antagonist (IL-1RA) to accelerate wound healing in mesenchymal stem cells [225]. Also, compared to murine 4T1.WT TNBC cells, CM from Cav-1KO revealed reduced expression of exosome markers including Annexin V and Alix in the EVs [8]. In this study Cav1KO was shown to mitigate lung metastasis as compared to the 4T1.WT in a murine TNBC model. Collectively, these reports highlight a crucial role of Cav-1 in regulating the EV generation, EV cargo sorting, and EV secretion.

In summary, the role of Cav-1 in metastasis is cell-specific and context-dependent. During the early malignant transformation stage, the levels of Cav-1 decrease. As the tumor progresses, loss of E-cadherin and EMT transition induces a 'permissive' cellular context that results in an upregulation of Cav-1 and increased pY14Cav-1. The pY14Cav-1 through interaction with its binding partners enables cell migration and metastasis (Fig. 2).

Clinical relevance of Cav-1 in BC

To understand the relationship between Cav-1 and BC regulation, Sloan et al. [163] analyzed 429 tissue sections from BC patients with a mean age of diagnosis at

61 years (range 33 – 97 years) and TNM (tumor, node, and metastasis) stage distribution at stage I, 22%; stage II, 53%; stage III, 17%; and stage IV, 2% of the patients [163]. In this study, the samples were classified as 8% ductal, 9% lobular, 3% medullary, and 10% other subtypes. Based on the intensity of staining for Cav-1, the samples were scored as negative (268/429, 63%), weakly immunoreactive (130/429, 30%), and strongly positive (31/429, 7%) for Cav-1 expression [163]. Although the study reported a positive correlation between Cav-1 expression and lower TNM stage, the presence of tumor epithelial Cav-1 did not relate to the disease prognosis [163].

Consistently, a comprehensive study that included 5, 926 patients with an average of 312 per study to a total of 19 studies failed to link the expression of Cav-1 as a BC prognostic marker [226]. In contrast, immunohistochemical staining for Cav-1 of 32 IDC samples from BC patients resulted in high (22/32, 68.75%) and low (10/32, 31.25%) scores for Cav-1 expression [132]. In addition, Cav-1 was found to be highly expressed 8/11, 72.72%) in the tumor tissue as compared to the adjacent nontumor section in $HER2^+$ BC patients [132], however, due to the limited sample size of 32, this interpretation may not be reliable. In normal breast tissue, CAV-1 was expressed in myoepithelial cells, endothelial cells, and a subset of fibroblasts. Luminal epithelial cells showed negligible staining. Cav-1 was expressed in 90% (out of 39) metaplastic breast carcinomas and 9.4% (out of 245) invasive BCs. In the later cohort, CAV-1 expression was significantly associated with 'basal-like' immunophenotype and with shorter disease-free and overall survival on univariate analysis. CAV-1 gene amplification was found in 13% of cases with strong CAV-1 expression.

Interestingly, several studies have reported stromal Cav-1 expression to be a better determinant of BC prognosis [161–168]. Stromal Cav-1 positivity reflected a 10-year survival rate of up to 91% as compared to 43% of patients lacking Cav-1 in the tumor stroma [163]. As previously mentioned [168], depletion of stromal Cav-1 expression was linked to a worse overall survival in basal-like TNBC patients, thus implicating the role of stromal Cav-1 in BC prognosis.

Anti-Cav-1 based cancer therapies

Although Cav-1 is a critical determinant of BC metastasis, strategies to target Cav-1 have been inadequately explored. In one interesting pharmacological strategy, activation of potassium channel Kv11.1 that was uniquely expressed in MDA-MB-231 cells by activator molecule (NS1643, PD115087) lead to calcium-dependent stimulation of tyrosine phosphatase 1B, PTP1B [227]. As a result, Cav-1 was dephosphorylated at Y14, thereby enabling β-catenin accumulation at cell borders to promote cell–cell adhesion and reduction in FA dynamics and cell motility [227]. In a different study, Wang et al. [228] demonstrated that ursolic acid, the bioactive compound of Oldenlandia diffusa, suppressed the proliferation and metastasis in xenograft zebrafish model of human TNBC by altering the metabolic abnormality. Mechanistically, ursolic acid induced the expression of Cav-1 by activating transcription factor, SP-1 [228]. Consequently, the binding of SP-1 to GC boxes (GGGCGG) within the promoter region of Cav-1 transcriptionally induced its expression. Since Cav-1 has a regulator role in the glycolytic switch [69, 178], it may be speculated that SP1/Cav-1 pathway activation modulates glycolysis, and that Cav-1 is a druggable target for screening glycolytic inhibitor candidates.

Similarly, betulinic acid (BA) has been reported to inhibit aerobic glycolysis in MCF-7 and MDA-MB-231 BC cells by targeting Cav-1/NF-κB/c-MYC pathway [229]. In this study, it was demonstrated that the inhibition of glycolysis by BA was through the upregulation of Cav-1, whilst depleted levels of Cav-1 failed to induce such an effect. Metformin, an anti-diabetic medication, has been shown to enhance the efficacy of trastuzumab emtansine (T-DM1) in $HER\text{-}2^+$ metastatic BC by promoting Cav-1 expression. Pretreatment with metformin induced Cav-1 overexpression, which enhanced T-DM1 internalization and drug sensitivity. This approach highlights the potential of metformin in improving T-DM1 clinical efficacy through Cav-1-mediated endocytosis [230].

(See figure on next page.)

Fig. 2 Role of caveolin-1 in breast cancer progression. **A** The ability of Cav-1 to regulate BC progression is cell-specific and context-dependent. In BC, Cav-1 expression is reduced during the early stages of malignant transformation. As the tumor develops, loss of E-cadherin induces EMT transition to alter the cellular context. The permissive cellular context allows upregulation of Cav-1 with increased phosphorylation, pY14Cav-1. The pY14Cav-1 acts as a docking molecule to promote cell migration, invasion and metastasis via Rho/ROCK pathway. **B** Remodeling of stromal fibroblast in TME during BC progression involves transformation of naïve fibroblasts to cancer-associated fibroblasts. Downregulation of Cav-1 in CAFs enables rapid cell proliferation, autophagy, resistance to apoptosis, and increase in the tumor volume. Collectively, these events contribute to tumor progression and metastasis

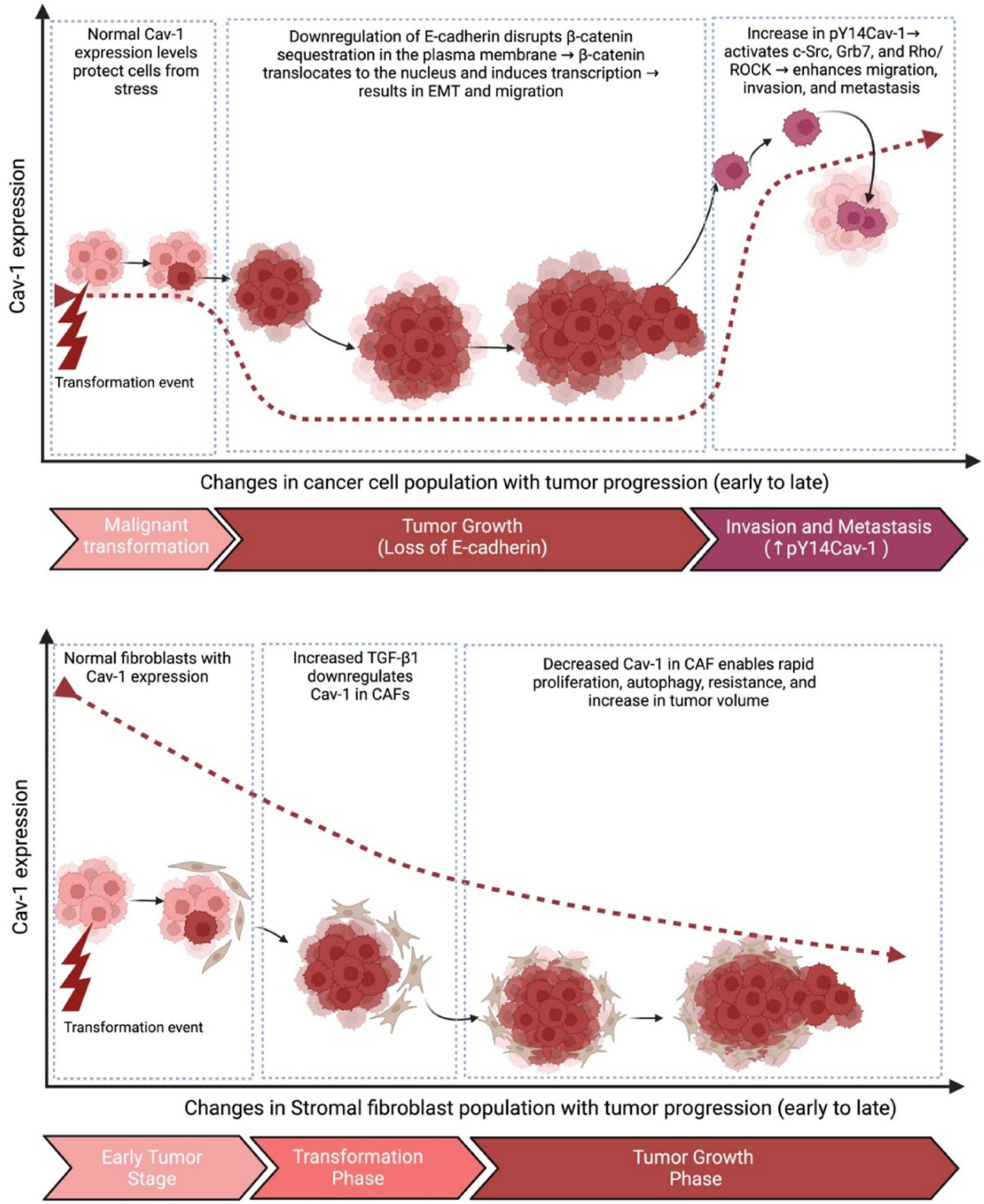

Fig. 2 (See legend on previous page.)

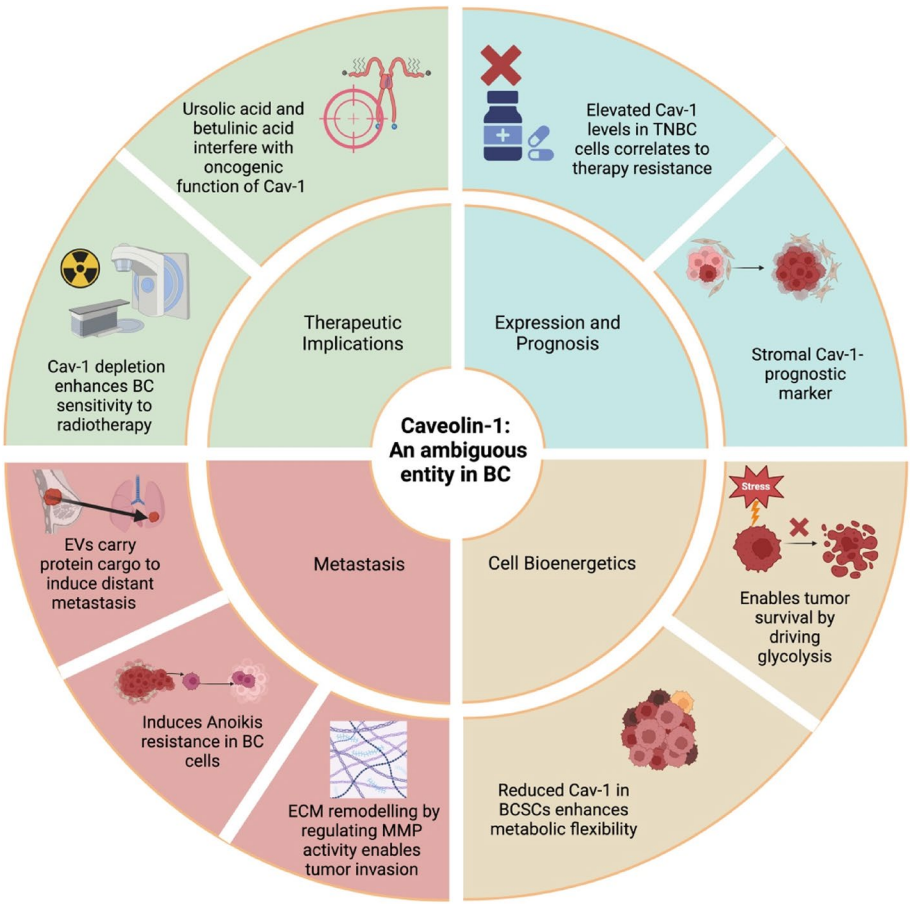

Fig. 3 Caveolin-1: An ambiguous entity in breast cancer: The role of Cav-1 in BC progression is depicted. Cav-1 is implicated in a myriad of events including ranging from cellular bioenergetics to the onset of BC metastasis. Owing to its cell-specific and context-dependent role, strategies to target Cav-1 should be carefully interrogated

Research on Cav-mediated internalization of Fmoc-FF nanogels in SKBR3, MDA-MB-231, MDA-MB-361, and MDA-MB-453 BC cells may provide further insights into the role of Cav-1 in cancer treatment [231]. These nanogels with a diameter of approximately 130 nm and a zeta potential of −20.0/−25.0 mV, enter cancer cells via caveolae-mediated endocytosis, especially those that overexpress Cav-1, for instance, MDA-MB-231 to induce selective cytotoxicity [231]. Despite the advances, anti-Cav-1 targeted cancer therapies have limitations because of the heterogeneity of Cav-1 expression in BC.

Concluding remarks

This review highlights what Cav-1's function initially suggested; that Cav-1 is a protein component of the caveolae, linking several signaling pathways to BC. Whilst Cav-1 is implicated both as a tumor promoter and a suppressor, any theory that implicates its role in BC is subject to this qualification. Herein, we discussed multiple mechanisms explaining this duality. Our view is that the dual activity of Cav-1 is based on the presence or absence of certain proteins depending on the subtype of BC. For instance, tumor suppression by Cav-1 in ER-positive BC is linked to its negative regulation of CAPER, nonetheless, in TNBC an upregulation of Cav-1 enhanced the disease progression. Likewise, the upregulation of Cav-1 in tumor epithelial cells results in enhanced GLUT3 expression and lactate production via AKT signaling, whereas its downregulation in the surrounding stroma increases aerobic glycolysis to provide nutrients to the tumor epithelial cells. Taken together, these highlight a complex role for Cav-1 in BC progression and most importantly do so in a context-specific fashion. Next, we focused on discussing the role of Cav-1 in BC metastasis. In this respect, several mechanisms have been illustrated to highlight the role of Cav-1 in metastatic cascade including ECM interactions, acquisition of invasive potential, anoikis resistance, and PMN formation. Furthermore, several

comprehensive studies involving BC patients documented that expression of Cav-1 can regulate BC, highlighting the fact that Cav-1 is a clinically relevant target in combating metastatic BC. Finally, strategies to target Cav-1 have been discussed, nonetheless, their merits must be carefully interrogated due to the complex and context-specific role of Cav-1 in the tumor type (Fig. 3). Since CSD of Cav-1 interacts with binding partners to regulate fundamental pathways including PI3K/Akt, MAPK, and Rho/ROCK signaling, an inhibitor to CSD may alter the downstream cascade with a potential to inhibit BC progression. Alternatively, genetic manipulations may alter the binding conformation of CSD. Since Cav-1 is implicated in EV cargo sorting, use of genomics and proteomics to delineate the cargo may provide insights into complex cellular mechanisms that augment premetastatic niche formation. Overall, findings from the proposed studies may provide potential anti-Cav-1 therapy for BC treatment.

Abbreviations

ADC	Antibody drug conjugate
AP-1	Activator Protein -1
BC	Breast cancer
BCSCs	Breast cancer stem-like cells
CAF	Cancer-associated fibroblast
CAPER	Co-activator of AP-1 and ER
CAV-1	Caveolin-1
CM	Conditioned medium
C-MAD	Caveolin membrane attachment domain
COX-2	Cyclooxygenase 2
CSD	Caveolin scaffold domain
CSK	C-terminal Src kinase
DCIS	Ductal carcinoma in situ
DPPIV	Dipeptidyl peptidase IV
ECM	Extracellular matrix
EGF	Epidermal growth factor
EMT	Epithelial-mesenchymal transition
eNOS	Endothelial nitric oxide synthase
ER	Estrogen receptor
EVs	Extracellular vesicles
FAK	Focal adhesion kinase
HER2	Human epidermal growth factor receptor
IBC	Inflammatory breast cancer
ICAM	Intercellular adhesion molecule
IDC	Invasive ductal carcinoma
ITG	Integrin
LRP6	Lipoprotein receptor-related protein
LAR	Luminal androgen receptor
MAPK	Mitogen activated protein kinase
MEFs	Mouse embryonic fibroblasts
MET	Mesenchymal-epithelial transition
MMPs	Matrix metalloproteinases
MnSOD	Manganese-dependent superoxide dismutase
NACT	Neoadjuvant chemotherapy
NF-kB	Nuclear factor kappa of B lymphocytes
OMV	Outer membrane vesicle
OS	Oxidative stress
PFK	Phosphofructokinase
PMN	Premetastatic niche
RA	Rheumatoid arthritis
STAT5a	Signal transducer and activator of transcription 5a
T-DMI	Trastuzumab emtansine
TLR4	Toll-like receptor 4
TMD	Transmembrane domain
TME	Tumor microenvironment
TNBC	Triple-Negative Breast Cancer
TNM	Tumor Node and Metastasis
VHL	Von Hippel-Lindau

Authors' contributions

NC,DP, BS wrote initial draft and prepared figures, DR, SA and JF finalized the draft and figures.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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